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### **Outbreak of Dengue Fever in Karachi 2006: a clinical perspective**

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#### **Abstract**

**Objective:** This study reports clinical manifestations and spectrum of severity of dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) in adult patients admitted during 2006 outbreak in Karachi. A rough estimation of cost of care was also calculated.

**Methods:** A cross-sectional study was done at a tertiary care hospital in Karachi from January to December 2006. Patients suspected of having DF with positive dengue IgM antibodies were included and records were reviewed. Patients were divided into DF, DHF and DSS as per WHO classification, and the severity of clinical manifestations was determined.

**Results:** A total of 278(65.72%) of 423 patients admitted with suspected dengue illness had positive IgM titer. Mean age was 31±12.9 years, with 168(60%) males and 110(40%) females. Common presenting symptoms were fever (100%), vomiting (78%), epigastric pain (52%), bleeding tendencies (34%), and erythematous rash (33%). Thrombocytopenia (60%), Leucopenia (45%), elevated transaminases (ALT 71%; AST 88%), and deranged PT (22%) and aPTT (75%) were the predominant.

**Laboratory parameters:** DF was diagnosed in 169(61%) patients, 82 (29%) were classified as DHF, and 27(10%) as DSS. Patients with DHF/DSS were younger <30 years (n=60, 55%) and had longer hospital stay (p=0.001). Case fatality rate for DHF/DSS group was 4.6%.

**Conclusion:** It was estimated that endemicity of DF is on the rise in Karachi and a significant proportion of patients had DHF and DSS. Younger patients develop DHF and DSS and have high case fatality rate (JPMA 59:339; 2009).

## Introduction

Over the last few years dengue has become a major international health problem affecting tropical and subtropical regions around the world, especially in urban and peri-urban areas. It is the most common arbovirolos in the world and also the most important one in terms of morbidity and mortality.<sup>1</sup> The World Health Organization (WHO) estimates that more than 2.5 billion people are at risk of dengue infection.<sup>2</sup>

Dengue fever is an acute infectious disease caused by an arbovirus in the Flavivirus genus. The disease manifestations range from a flu like illness known as dengue

**Table-1: WHO criteria for diagnosis of Dengue fever, Dengue hemorrhagic fever, Dengue Shock Syndrome.**

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### **Probable Dengue Fever (DF)**

Acute febrile illness with 2 or more of the following manifestations:

1. Headache
2. Retro-orbital pain
3. Myalgia
4. Arthralgia
5. Rash
6. Haemorrhagic manifestations
7. Leucopenia; and Supportive serology; or

Occurrence at the same location and time as other confirmed cases of dengue

### **Confirmed DF**

Case confirmed by laboratory criteria (isolation of the dengue virus, 4-fold or greater change in antibody titers, demonstration of the dengue virus antigen or genomic sequence).

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### **Dengue Haemorrhagic Shock (DHF)**

All of following must be present

1. Confirmed dengue fever through laboratory
  2. Fever for 2-7 days
  3. Bleeding evidenced by at least one of the following:
    - a. Positive tourniquet test (TT),
    - b. Petechiae, ecchymosis, or purpura,
    - c. Bleeding from the mucosa, gastrointestinal tract, injection sites or others.
    - d. Haematemesis or malaena
    - e. Thrombocytopenia ( $100,000/\text{mm}^3$  or less),
    - f. Evidence of plasma leakage due to increased vascular permeability,
  4. Permeability, manifested by at least one of the following:
    - a. Rise in the haematocrit  $\geq 20\%$  above average for age, sex, population.
    - b. Drop in the haematocrit following volume-replacement treatment  $\geq 20\%$
    - c. Signs of plasma leakage e.g., pleural effusion, ascites, hypoproteinaemia
- 

### **Dengue Shock Syndrome (DSS)**

1. Four criteria of DHF
  2. Plus signs of circulatory failure manifested as
    - a. Rapid and weak pulse
    - b. Narrow pulse pressure ( $<20\text{mmHg}$ )
    - c. Hypotension for age (Sys Press  $<80\text{mmHg}$  for  $<5\text{yrs}$ ,  $<90\text{mmHg}$  for  $>5\text{yrs}$ )
    - d. Cold, clammy skin
    - e. Restlessness
- 

fever (DF) to a severe and at times fatal disease characterized by haemorrhage and/or shock, known as dengue haemorrhagic

fever/dengue shock syndrome (DHF/DSS). There are four viral serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). The virus transmits from viraemic to susceptible humans mainly by bites of the *Aedes aegypti* and *Aedes albopictus* mosquito species.<sup>3</sup> In Southeast Asia, DF is a disease of childhood. There is, however, evidence to suggest that the incidence of DHF among adults is increasing.<sup>4</sup> DHF is a life threatening complication of dengue infection manifested by high fever of 2-7 days, haemorrhagic phenomena, and thrombocytopenia. Some patients may progress to shock known as DSS. If the illness is not identified early in the course and not treated promptly when indicated, case fatality rates (CFRs) of DHF can go over 20 per cent and that of DSS can be as high as 44 %.<sup>5</sup> Severe illness among adults with higher CFRs has already been reported from India and Bangladesh.<sup>6</sup>

In Pakistan the first out break of DF was observed in 1994.<sup>7</sup> In the subsequent years sporadic cases of suspected dengue infection were reported. During the last few months of 2005, we began to see more than usual number of patients with undifferentiated fever and thrombocytopenia. Many patients were found to be positive for dengue IgM. Few had unexplained encephalitis, fulminant hepatic failure, disseminated intravascular coagulation and haemorrhage. This study was undertaken to determine the severity of clinical manifestations of DF and DHF/DSS in adult patients. We also studied the predictive markers for severity of the disease and estimated the average cost of management of different subsets of patients in a tertiary care referral centre.

## Patients and Methods

This cross-sectional study was undertaken in the Medical unit of Aga Khan University Hospital (AKUH) Karachi, Pakistan from January 1st to December 31st, 2006. A total of 423 patients were hospitalized with suspicion of dengue infection.

Two hundred and seventy eight patients, who had acute febrile illness, a positive test for dengue IgM antibodies by standard serological test of ELISA technique and with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, leucopenia, and haemorrhagic manifestations were incorporated as cases of dengue. Informed consent was taken from all the patients or their relatives (next of kin) before enrolling them into the study. Clinical, haematological and biochemical findings were recorded serially until discharge. Sera from all suspected cases were tested for dengue IgM antibodies after 5-6 days of fever in the main laboratory of the hospital. Enteric fever was ruled out by performing blood cultures where indicated. Malaria and sepsis were excluded by peripheral thick and thin film examination and/or immuno-chromatographic antigen detection for malaria (ICT) and blood cultures for sepsis respectively. The WHO classification and case definitions were used to classify the

disease as DF, DHF and DSS.<sup>8</sup> Refer to Table 1.

A chest radiograph was obtained in individuals with clinical suspicion of a pleural effusion. Where indicated complete blood count and abnormal coagulation profile were repeated on daily basis to monitor deterioration/improvement. Ultrasound of abdomen was performed in patients with marked abdominal tenderness. Patients were followed up and their outcome was noted.

### Calculation of Cost of Care:

Aga Khan University Hospital is one of the largest private sector health care facility in the metropolitan city of Karachi. It serves as a tertiary-care referral centre that is equipped with exceedingly modern health care facilities and able to handle the most sick and serious patients. Being a private hospital, however, the cost of treatment is significantly higher than that of hospitals in Government sector. . Information about the approximate cost of care of different subsets of patients was taken from patient benefit services department. A rough estimate was calculated by the financial counselor based on following components:

#### 1. Approximate length of stay:

This was determined by taking into account the initial diagnosis and anticipated management plan.

Estimated Length of Stay (Bed charges X # of days & daily professional fees X # of days).

#### 2. Involvement of ICU/SCU:

An average per day charges for SCU is 12k to 18k and for ICU 20k to 35k.

3. Major Investigations (if any) (Listed charges).

4. Expensive Pharmacy (if any) (Listed charges).

### Statistical Analysis

All variables were entered into Statistical Package for Social Sciences (SPSS) version 14.0. Means and standard deviations were calculated for continuous variables and frequencies for categorical variables. Cross tabulation was done to determine relationship between different variables and p-values were calculated as the test of significance. Student's t-test was used to analyze continuous variables in demographic and clinical data. The clinical manifestations and laboratory findings of each group of illness were compared using the chi-square or Fisher's exact test for proportions and analysis of variance (1-way ANOVA) for continuous data.

### Results

During the study period, from 1st January to 31st December 2006, 423 patients were admitted with suspected dengue infection. Of these dengue viral infection was confirmed in 278 (66%) by positive dengue IgM results. Their ages ranged from 15 to 72 years with a mean age of  $31 \pm 12.9$  years. The male to female ratio was 1.5:1 with 168 (60%) males and 110 (40%) females. Average hospital stay was 3.5 days. The frequency of cases varied in different months. Most of the cases were seen in months of August, September and October. 267 patients were residents of Karachi. Seven patients (2.5%) were referred from other parts of the Sindh province, while three patients were from Punjab. Within the town, most of the cases were from the east, center and north

Figure 1: Area-wise Distribution of Dengue Patients.

of Karachi.

Two hundred and fifty six (92%) patients were admitted through the Emergency Room (ER) while the rest 22 (8%) attended the consulting clinics and were hospitalized. Fever was the most common clinical presentation, found in all patients on presentation (100%).

The most frequent haematological abnormality overall was severe thrombocytopenia (platelet count <50,000/mm<sup>3</sup>) in 167 (60%) patients. Other abnormalities included Leucopenia in 124 (45%) patients, elevated transaminases; ALT in 149 (53.5%); AST in 156 (56%) and abnormal renal function (serum creatinine >1.5 mg/dl) in 68 (24.5%). Deranged PT (>14 seconds against control of 12 seconds) was seen in 57 (20.5%), deranged aPTT (>35 seconds against control of 30 seconds) in 81 (29%) and hyponatremia (Na<sup>+</sup>?130mEq/L) in 36 (13%) patients, mainly belonging to DHF and DSS groups. Twelve (4%) patients had concomitant malarial (vivax and/or falciparum) infection. These patients received antimalarial treatment along with symptomatic and supportive therapy for dengue infection. All had uneventful recovery. Blood cultures were done in 72% patients. Only 2 patients had positive results (E. coli and Acinetobacter). They died of septic shock. Abdominal ultrasound examination was requested in 27 patients; 37% had gall bladder wall thickening consistent with

acalculous cholecystitis.

There were a total of 109/278 (39%) patients with DHF/DSS. Out of these 82/109 (75%) patients of dengue virus infection met the criteria for DHF and 27/109 (25%) qualified for DSS. The male to female ratio was 1.9:1 in DF and 1:1 in DHF/DSS groups. Age range with the highest percentage of cases was 21 to 30 years for both DF (31%) and DHF/DSS (33.9%). Only 9 (8.2 %) cases of DHF/DSS were seen in patients above 50 years of age. Hospital stay was greater than 3 days in most of the DHF/DSS cases, i.e., 83.5% as compared to DF, 65.7% cases (p=0.001).

Among 109 DHF/DSS patients mean platelet count was 67,000 ±59,900. Mean haematocrit was 39.7 ±6.0% and ranged from 19.2% to 55.5%. PT and aPTT were checked in 66 (60.5%) cases. PT was abnormal in 15 (13.8%) patients. However, derangement of aPTT was more commonly observed in DHF/DSS as compared to DF cases (40.3% Vs 33.7%, p=0.044).

Mean ALT in DHF/DSS was 274 ±646 while highest level of AST was 10,065 IU/L (Mean 607; SD±1434). DHF/DSS cases had significantly higher levels of AST (p=0.017) and ALT (p=0.022) as compared to DF cases (Mean AST 265, SD±331, Mean ALT 134, SD±164). High ALT (> 100 IU/L) [odds ratio (OR), 1.00; 95% Confidence interval

**Table 2: Descriptive characteristics of patients diagnosed with dengue virus infection.**

	DF (n=169) %	DHF/DSS (n=109) %	Overall (n=278) %	'p'-value
<b>Clinical Signs/Symptoms</b>				
Facial Flushing	3 (2%)	4 (3%)	7 (2.5%)	0.438
Sore Throat	27 (16%)	14 (13%)	41 (15%)	0.495
Epigastric Pain	85 (50%)	61 (56%)	146 (52.5%)	0.390
Restlessness	1 (1%)	2 (2%)	3 (1%)	0.282
Headache	23 (14%)	13 (12%)	36 (13%)	0.427
Bone/Muscle Pain	53 (31%)	24 (22%)	77 (28%)	0.117
Retroorbital Pain	0	1 (1%)	1 (0.3%)	0.210
Nausea/Vomiting	134 (79%)	83 (76%)	217 (78%)	0.409
Diarrhea	10 (6%)	2 (2%)	12 (4%)	0.05
Chills	129 (76%)	60 (55%)	189 (68%)	<0.001
Hepatomegaly	1 (1%)	1 (1%)	2 (0.7%)	1.00
Hypotension	0	26 (24%)	26 (9%)	<0.001
Tachycardia	11 (6%)	7 (6%)	19 (7%)	1.00
Tachypnoea	6 (3%)	2 (2%)	8 (3%)	0.487
Skin Rash	55 (32%)	37 (24%)	92 (33%)	0.896
Lymphadenopathy	0	2 (2%)	2 (0.7%)	0.153
Bleeding	6 (3%)	89 (81%)	95 (34%)	<0.001
<b>Laboratory Parameters</b>				
Raised Haematocrit (≥ 50)	8 (5%)	26 (24%)	34 (12%)	0.423
Leucopenia (<4)	75 (44%)	49 (45%)	124 (45%)	0.714
Raised Alk. Phosp	7 (4%)	4 (4%)	11 (4%)	1.00
Raised AST (>3times)	57 (34%)	38 (35%)	95 (34%)	0.461
Raised ALT (>3times)	34 (20%)	32 (29%)	66 (24%)	0.207
Raised PT (>14 sec)	37 (22%)	20 (18%)	57 (20.5%)	0.532
Raised aPTT (>35 sec)	43 (25%)	38 (35%)	81 (29%)	0.044
Raised Creatinine (>1.5)	14 (8%)	6 (5.5%)	20 (7%)	0.677
Hyponatremia (<130)	25 (15%)	11 (10%)	36 (13%)	0.221
Thrombocytopenia (<105)	141 (83%)	91 (83%)	232 (83%)	0.636

P-value < 0.05 is considered significant.

(CI), 1.0 to 1.003;  $p=0.04$ ] and aPTT (OR 1.03, CI 1.004 to 1.06,  $p=0.02$ ) were found to be significantly associated with DHF/DSS cases.

For details of laboratory parameters of the three groups refer to Table-2.

Five patients died in the DHF/DSS this group. Two had DHF and three went into shock (DSS). The case fatality rate was 4.6%. There was no mortality in patients with DF. Out of five, four patients died of dengue virus infection itself. All four presented with fever, myalgia and petechiae. 2 of the 4 patients died of profound shock. One had severe hepatitis (AST 10065 IU/L; ALT 2325 IU/L) and multi-organ failure. Two patients had concomitant bacterial infection (E.Coli in blood culture) and died of sepsis. Out of five only one had associated comorbidities of diabetes and COPD.

All patients received symptomatic and supportive treatment including intravenous fluids, antiemetics and antipyretics. Blood and blood products, antibiotics and inotropic/vasopressor support were administered as and when required. Of DF patients, 53/169 (31%) received prophylactic platelet transfusion when their platelet counts dropped to  $<20,000$ ; 42/109 (38%) patients in DHF/DSS group required platelet transfusion. Fresh frozen plasma was infused in 10 (9.2%) of DHF/DSS patients with DIC and overt bleeding. Two pregnant females with 22nd and 31st weeks of gestation had DHF and recovered fully with no apparent harmful effects on the pregnancy. Two hundred and seventy three (98%) patients recovered completely with over all mortality rates of almost 2%. Five patients died two because of profound shock, one developed acute liver failure and the other two had concomitant sepsis and co-morbid conditions like diabetes mellitus and chronic lung disease.

### Cost of Management:

We estimated that the average cost of management of a patient with DF varied from 20,000 to 40,000 PKR. In case, the patients requiring critical care stay (DHF/DSS cases); the cost was as high as 150,000 to 200,000 PKR for 3-4 days.

### Discussion

In Karachi, DF has been recognized as one of the causes of fever since 1994 when the 1st major outbreak of DHF occurred over here. Very few cases were seen until September 2005. Thereafter up to December major hospitals of the city reported a rapid increase in the number of cases of probable dengue infection. Very few were laboratory confirmed cases. 2006 outbreak is considered to be the largest epidemic of dengue in Karachi. Our study reports the clinical profile of the IgM confirmed cases. DHF is considered to be a disease of paediatric population and now a leading cause of hospitalization and death among children.<sup>9</sup> In our study, 80%

of patients with DHF/DSS were below 40 years (mean  $26 \pm 7.5$  years). This observation is consistent with reports from other endemic countries. Gupta et al<sup>10</sup> from India showed a maximum number of cases between the ages of 21 and 30 years. Likewise in Singapore 2005 outbreak, young adults were predominantly affected by DHF.<sup>11</sup> Peak incidence is

Number of Cases

Figure 2: Monthly distribution of Dengue cases.

noted in August, September and October (Figure 2). The reason for this is not entirely clear. One explanation can be the heavy rains of monsoon season, which usually start in July and August, resulting in stagnant water that serves as breeding ground for vectors of this virus. Hot summer seasonal peak is also reported in studies from India and Bangladesh.<sup>10,12</sup>

Presenting symptoms of fever, nausea/vomiting, epigastric pain, bleeding tendencies and laboratory features of thrombocytopenia, elevated liver enzymes, deranged PT/aPTT were not different from other studies.<sup>13,14</sup> Hepatic dysfunction and bleeding from the gastrointestinal tract secondary to associated coagulopathy are manifestations of severe dengue infection.<sup>15</sup> Most of our DHF/DSS patients had abnormal levels of AST and ALT as compared to DF. Liver injury from dengue virus is mediated by its direct infection of hepatocytes and Kupffer cells.<sup>16</sup> Marked hepatic dysfunction has been documented in severe cases.<sup>17</sup> Disseminated intravascular coagulation, which occurs in DHF/DSS patients and consumes both platelets and clotting factors, may contribute to the prolongation of aPTT. Therefore, elevated aPTT and prolongation more than twice the control may serve as a marker for dengue shock syndrome.

The over all CFR in the Southeast Asia region is now less than 1%.<sup>18</sup> However, rates vary significantly between countries and hospitals. In this study mortality was 4.6% in patients belonging to the DHF/DSS group, which is

comparable with other regional studies.<sup>13,19</sup> It means that early diagnosis, appropriate investigations, strict monitoring, and prompt management could help in reducing mortality in dengue haemorrhagic fever. Increase in dengue mortality is considered to be a reflection of the increase in the proportion of DF patients who develop DHF/DSS. Dengue serotype 3 generally causes more severe infection. Serum samples from suspected DHF/DSS cases in a small epidemic of 2005 revealed DENV-3 as the cause of the DHF.<sup>20</sup> High mortality in our patients may be a reflection of re-infection, infection with a virulent viral serotype, late presentation to the hospital and lack of uniformity in patient management because of relatively recent introduction of dengue in our population.

Frequency of DF outbreaks is likely to increase in Pakistan in conjunction with increasing numbers of cases of severe disease and high indices of the principal mosquito vector *Aedes aegypti*. Epidemics of DHF/DSS may therefore become an increasingly important public health problem in Pakistan. One important aspect of any illness is cost of treatment. Being an economically underprivileged country where the individual patients have to bear the cost of health care, the financial implications of the disease management are worth taking into consideration. In addition to vector control, key health sector response for reduction of mortality and morbidity lies primarily in two areas: early detection of cases and improved & cost effective management of patients. Mortality in excess of 1% may be considered the consequence of inadequate care, late diagnosis and delayed hospitalization. A hospital-based study during the dengue outbreak in Delhi revealed that mortality could be very low in patients who came early to the hospital.<sup>21</sup> Late presentation was also strongly associated with increased mortality in children with DHF in the Philippines.<sup>22</sup>

The study confirms the epidemic of DF in this region. Karachi is the largest city of the province with more than 15 million people; most of who are living in poorly built houses with lack of water and solid waste disposal. Effective disease prevention programme should include vector control by chemical, biological or environmental measures, mass education programmes of the community to seek early medical care and strengthen the knowledge of family physicians/general practitioners to recognize the warning signs of the disease.

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